EXHIBIT 2

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

IN RE: ETHICON, INC. PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LIGITATION	**Master File No. 2:12-MD-02327** **MDL No. 2327**
THIS DOCUMENT RELATES TO PLAINTIFFS: **Wave 1 Cases**	**JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**

RULE 26 EXPERT REPORT OF PROF. DR. MED. UWE KLINGE

I. BACKGROUND AND QUALIFICATIONS

With regard to my medical training, I attended medical school in Aachen, Germany from 1977 to 1983. I began my medical profession at the surgical department of the University Hospital of the RWTH, Aachen, Germany (Department heads/Mentors: Prof. Reifferscheid - 1985, Schumpelick 1985-2010, Neumann 2010). From 1995 to 2006, my practice was focused primarily on abdominal surgery, and specifically, hernia repair. As a hernia surgeon, I used textile implants (flat meshes) for the repair of abdominal wall hernia or defects in more than 300 patients mainly groin hernia, umbilical hernia, incisional hernia and parastomal hernia. Although I never performed surgery for repair of SUI or POP, I implanted and studied the mesh used in TVT, Prolene, extensively. 1

In 1993, in addition to my surgical practice, I began focusing on surgical research in the area of biomaterial science including tissue engineering, material characteristics and designed preclinical models for surgical mesh and histopathology. I am the author/co-author of approximately 200 peer-reviewed publications listed in PubMed, over 100 of which involve hernia and/or surgical mesh. I have authored and/or contributed to more than 50 book chapters and have been an invited lecturer to more than 160 speaking engagements/conferences. I have received numerous research grants from various institutions and corporations including several grants from the German Ministry for Education and Research, the Ministry for Economics, the German research foundation DFG, the NRW Ministry for Education and Research, the Interdisciplinary Center for Clinical Research of the University (RWTH), as well as from industry (Ethicon, Covidien). (Attached hereto as Exhibit “A” is a current copy of my Curriculum Vitae with a list of my publications).

In 1994, we began looking at soft tissues and at the time, there was no information to help understand the cellular response to these materials. I then started to work with Dr. Bernd Klosterhalfen and together, we established a way to analyze soft tissue reactions in order to determine the difference between good materials and the best materials. This led to the ability to see the extent of inflammation, foreign body reaction and fibrosis a biomaterial will have on the soft tissue and how that will directly relate to numerous complications. After the method was established, it was found in many of our publications and in the publications of our peers.

II. BRIEF HISTORY OF TEXTILE MESHES FOR TISSUE REPAIR 1958-1993 – THE ABDOMINAL WALL

The current use of textile implants, so-called meshes, is based on Usher who, in 1958, started to publish the successful reinforcement of abdominal wall in six dogs. Initially, meshes were regarded as an alternative procedure, particularly in big hernias. In 1986, Lichtenstein presented his procedure of mesh implantation as the new standard for groin hernia repair. With this technique, the mesh reinforces the tissue in a so-called “tension free” manner. In the early years, Usher used a knitted structure of polypropylene, later on widely known as Marlex®. However, Marlex® had increased stiffness after implantation along with considerable complications. Alternatives to Marlex were the polyester mesh Mersilene® or the ePTFE from Gore.

In the late 1980’s and early 1990’s, when polypropylene surgical mesh was starting to be used in hernia surgeries, there was a general lack of knowledge about the materials and about the clinical outcomes associated with these materials. Side effects often manifested with a considerable delay of up to several years. Correspondingly, reports dealing with pain as a major postoperative complication (less than 10% of all hernia publications in PubMed) were published with a delay of years [Fig.1]. We began to look at the scar formation pathologically and developed the theory that incisional hernias could be due to a biological problem.

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III. DEVELOPMENT OF THE FIRST LARGE PORE MESH CONSTRUCTION THAT WAS ADAPTED TO PHYSIOLOGICAL REQUIREMENTS

In the early 1990’s, we speculated that an adaptation of the strength of surgical meshes to the physiological requirements of the tissues in which they would be implanted may allow a considerable material reduction which could improve biocompatibility. We felt that the textile characterization of meshes at that time did not sufficiently reflect the physicochemical properties of the textile, so we had to start almost from the beginning to first identify the relevant parameters.

RWTH University initiated a research program such that in conjunction with various grants, we could add some basic investigations to this project. Through cooperative efforts with Ethicon and the support by these research grants, the project went on for about 10 years. In this period, we gained significant knowledge about the textiles; we defined standard biomechanical characterization for better comparison; we established models for testing the tissue response in animals; we looked for parameters that reflected the inflammatory and fibrotic activity of the foreign body reaction; we developed a technique to quantify the biomechanical impact on, and the biomechanical properties of, tissues.

As our research progressed, we calculated that hernia meshes needed a tensile strength of 16 N/cm and an elasticity of about 20-30% at this strain [Fig. 2]. Ethicon provided our research team with thin (about 40 μm) polypropylene threads. Because we were provided only with these 40-μm fibers, we had to combine 5 strands of them at interval distances of 2-3 mm to withstand a strain of 16 N/cm. As this polypropylene net was very floppy, we added an absorbable fiber of Vicryl® (Ethicon) to temporarily make it stiffer. After absorption of the Vicryl®, there would remain just an open structure, with about 30% of the material of the Marlex®. This new structure with pores larger than 2 mm, later marketed as Vypro® by Ethicon (1998), was then studied extensively in several experimental studies. The results were presented at several conferences and most of it has been published in PubMed-listed journals.

In the 1990's, the mesh proponents were convinced that the problem of recurrence had been solved, that the outcome was not affected by the type of material used and that mesh-related complications were essentially nonexistent but occurred mainly as a result of surgical technique or patient co-morbidities. However, our extensive surgical mesh research over twenty-years, including our research, with Ethicon, demonstrates that these opinions are incorrect.

IV. BIOMECHANICS

The main task of biomaterials used for surgical repair is to strengthen the tissue in which it is implanted and to restore its function. Specific to pelvic organ prolapse, the primary task of the prosthetic is to strengthen the pelvic floor tissues and to restore the pelvic anatomy and function. The mesh should mimic as closely as possible, and be integrated physiologically into, the tissues of the pelvic floor based on a maximum biocompatibility. Such surgical biomaterials should be without serious long-term complications such as recurrence, erosion, infection or chronic pain, and should have optimal handling characteristics for an easy, comfortable and safe repair.

Ethicon's professional education team communicated what it considered to be the "ideal" mesh requirements for pelvic floor repair to physicians that were being trained by Ethicon in the Prolift technique. They stated to physicians that the "ideal" vaginal graft should "be histologically well tolerated (inert), resist infection, be easily handled and implanted, incorporate into surrounding tissues, resist mechanical stretch, not shrink, and recreate and maintain the physical characteristics of the supple and distensible vaginal wall."[1] [2]

Ethicon was aware of the difficulties in defining the biomechanical requirements of the human pelvis. They admit in their internal documents regarding the biomechanical requirements of the pelvis that"…the ideal mesh for prolapse repair which mimics precisely the biomechanical needs of the pelvic floor region has not been developed."

Ethicon recognizes that:

> "…a recent major focus of mesh development and research is the patient's quality of life. Pain and discomfort can result from stiff mesh that were originally designed for hernia surgery and 'over-engineered' to exceed the

[1] ETH.MESH.00033325: Professional Education PowerPoint presentation titled "The Science of Augmented Extracorporeal Reconstructive Pelvic Surgery" in which the "Ideal Mesh" is described
[2] ETH.MESH.03906525 Graft or No Graft PowerPoint Presentation

> burst strength of the abdominal wall at the cost of losing compliance. Although limited data suggests that, in terms of anatomical and biomechanical outcomes, synthetic polypropylene meshes are superior to biologic meshes, there is significant evidence that the complications associated with synthetic meshes can cause significant morbidity including infection, erosion, exposure, and pain. In addition, the vaginal tissue to be augmented is often structurally compromised, atrophic, and devascularized. Such poor tissue quality increased the risk of poor tissue incorporation into the mesh potentially resulting in suboptimal healing and mesh exposure or erosion into an adjacent viscous. Moreover, there is evidence that meshes shrink in vivo leading to increased stiffness, pain and poor restoration of the normal properties of the vagina compliance. Research has demonstrated that bioprosthetic mesh implantation results in a scarring reaction and subsequent decreased compliance. An ideal quality of prosthetic mesh would be to mimic the compliance of the supported tissue thereby resulting in more comfort and function after implantation. To be able to define the most appropriate design parameters for the next generation of pelvic floor prosthesis it is important to generate an advanced understanding of the pelvic floor biomechanics and associated mechanical boundary conditions."[3]

Ethicon scientists recognized that the unique requirements in pelvic reconstructive surgery include the fact that 1) anatomically, the pelvis has a complex, 3-dimensional architecture and vector forces with little or no bony (and often pelvic floor muscle) reinforcement, and 2) functionally, the prosthetic must remain pliable as a result of pelvic organ filling/emptying, tissue pliability, and sexual function.[4] These and other Ethicon scientists also admitted that there is no descriptive model available to predict the mechanical behavior of pelvic mesh implants. Furthermore, Ethicon's Medical Affairs Director, Axel Arnaud, testified that Ethicon's claim that their pelvic floor meshes remain soft, supple and/or pliable was "an illusion".[5]

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Other employees at Ethicon, namely, those involved in regulatory and sales and marketing, told a different story. In the Prolene Soft 510(k), the Gynemesh PS 510(k), as well as in the Gynecare Prolift IFU, Ethicon claims that "the elastic properties of the mesh adapt to the various stresses encountered in the body." Ethicon admitted to the FDA in 2007 that they had no data to support this statement.[6] In its patient brochures for Prolift, Ethicon claims that the Prolift repair system is "a revolutionary surgical technique… [that] uses a soft synthetic mesh specially designed for placement through the vagina…"[7] However, the term "specifically designed" came to the attention of Mark Yale, WW Director of Risk Management during the development of the Prolift +M IFU. He stated that "this mesh was not 'specifically designed' for Prolift application, we pulled a mesh out of our existing bag of tricks."[8]

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[3] ETH.MESH.02010834-ETH.MESH.02010854: February 16, 2011 report written by Jurgen Trzewik and Christophe Vailhe titled "Biomechanical consideration for Pelvic floor mesh design"
[4] ETH.MESH.00033325: Professional Education PowerPoint presentation titled "The Science of Augmented Extracorporeal Reconstructive Pelvic Surgery" in which the "Ideal Mesh" is described
[5] Axel Arnaud Deposition November 15, 2013 68:10-69:13
[6] ETH-65881: Gynecare Prolift IFU
[7] ETH-00255: Ethicon Gynemesh PS 2006 marketing brochure
[8] ETH.MESH.00318775: Email dtd 5/08/08 from Mark Yale to Jennifer Paine, Jonathan

Dr. David Robinson, Medical Affairs Director at Ethicon, gave a Power Point presentation titled "Review of Surgical Techniques Using Mesh"[9] which was marked as Plaintiffs' Exhibit 519 of his deposition. The presentation states: "material science has been slow to meet the special requirements of the vaginal environment" and "The vagina is **NOT** the abdomen and it is not similar to any other surgical environment." When this portion of his presentation was discussed at deposition.[10] Dr. Robinson agreed that these are accurate statements.

Physiologic properties of pelvic tissue

The primary difficulty in developing a model to predict the mechanical behavior of pelvic mesh implants lies in the understudied and poorly understood characteristics of vaginal tissue. Drawing conclusions from studies involving animal tissues in an attempt to correlate those findings to the tissues in the human pelvis has severe limitations. As Ethicon has recognized, "[a]nimal models allow for controlled studies, which are useful in understanding the underlying factors that may contribute to the development and progression of human diseases by systematically examining confounding risk factors. However, the need to translate findings to the clinic is very important, and therefore understanding how these animal models relate to humans must be evaluated."[11] In fact, in the 2010 Preclinical Efficacy Assessment for Ethicon Gynecare Gynemesh M, it says, "There is no representative quadraped animal model of human vaginal prolapse." It then goes on to say that the most similar pelvic anatomy would be that of a baboon, but, "this species has not demonstrated the pathology of spontaneous pelvic organ prolapse" [12]

At the conclusion of our work in the development of Vypro hernia mesh with Ethicon, my colleagues and I published an animal study in which we demonstrated that the physiological forces of the abdominal wall could be quantified.[13] By properly defining these physiological forces for the first time, we were able to demonstrate how the animal model related to human in vivo behavior to improve the textile structure of hernia meshes, and thus, to improve the symmetrical distribution of the retaining forces in all directions. Compared with the considerable restriction of the abdominal wall mobility by Prolene (polypropylene) and Mersilene (polyester) meshes, there was no increase in the bending stiffness after the implantation of the new mesh in rodents. Histological examination showed a pronounced reduction of the inflammatory reaction in the tissues, and the collagen bundles were orientated merely around the mesh filaments instead of forming a scar plate that completely embedded the mesh. By adapting the design of the new hernia mesh to the physiological forces of the abdominal wall, we were able to reduce the amount of prosthetic material which caused less inflammation and less restriction in the mobility of the abdominal wall while retaining the required tensile strength of 16 N/cm.

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No similar, definitive studies have been conducted by Ethicon for the pelvic floor. Pelvic tissue is extremely complex; it has a non-linear stress-strain relationship, large deformation

Meek et al regarding Prolift mesh was "not specifically design".
[9] ETH.MESH.00396836: PowerPoint presentation created by David Robinson titled "Review of Surgical Techniques using Mesh"
[10] David Robinson Deposition Testimony from rough draft 293:13; 194:14
[11] ETH.MESH.02010834-ETH.MESH.02010854: February 16, 2011 report written by Jurgen Trzewik and Christophe Vailhe titled "Biomechanical consideration for Pelvic floor mesh design"
[12] ETH.MESH.04940233 – Preclinical Efficacy Assessment for ETHICON GYNECARE GYNEMESH M
[13] U. Klinge, et al., Modified Mesh for Hernia Repair that is Adapted to the Physiology of the Abdominal Wall; Eur J Surg 1998; 164: 951-960

before yield, is viscoelastic, inhomogeneous, anisotropic and, when trying to analyze the tissues upon explant, has changing vaginal tissue properties after removal from the body.[14] There have been a number of scientists and surgeons, Cosson, Rubod, Boukerrou, and Boulanger, just to mention a few, who have attempted through various studies to characterize the biomechanical behavior of human vaginal tissue. However, as is evidenced by their studies and acknowledged by Ethicon, "the reported vaginal tissue properties vary extremely for different investigators and different experimental setups; there is no consistent nomenclature for biomechanical properties established; and, the reported material parameters exhibit a strong deviation even between different patients, examined by the same investigators...more data is needed from humans to help us characterize the differences between normal and pathological tissues, as well as to help us identify appropriate animal models."[15,16]

Ethicon R&D engineer, Christoph Vailhe testified that newer manuscripts contain more reliable and definitive data regarding vaginal tissue properties including elasticity. However, a review of those manuscripts indicates that they actually continue to demonstrate ongoing debate and a lack of reliable and sufficient data concerning vaginal tissue properties. [17] [18] [19]

Christoph Vailhe further testified that "As of 2012, no validated animal model exists to evaluate mesh erosion in the pelvic floor or to determine the biomechanical forces of the pelvis".[20]

Apparently, Ethicon merely converted our work on new generation hernia meshes and repackaged it as pelvic meshes assuming, without justification, that a safe mesh design for hernia application equaled a safe mesh design for pelvic floor application. As injuries to numerous patients continue to mount, this assumption has proven dangerously faulty.

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For example, from October through December 2008, prior to Ethicon's launch of its new generation POP mesh, Prolift +M, there were required readings by the sales and marketing force to educate them regarding certain aspects of pelvic floor meshes before detailing the product with surgeons. These were known as "Prolift +M Pre-readings". Jonathan Meek, the Prolift +M team member in charge of sales and marketing, included in these readings the work that my colleagues and I had done ten years prior (reference above).

This leads me to a number of important observations: 1) Ethicon had not conducted their own studies on pelvic mesh that would have built upon the knowledge they had gained a decade prior in order to determine whether their pelvic floor meshes approximated the physiological forces in the pelvis; 2) four of the seven suggested articles were studies involving hernia meshes from the late 1990's and only two of the remaining studies involved vaginal tissue; and 3) Mr. Meek admitted in an email dated October 29, 2008 that "…up until recently, I was ignorant to the work

[14] ETH.MESH.03753245: PowerPoint presentation titled "Biomechanics (Pelvic Forces)"
[15] ETH.MESH.02010834-ETH.MESH.02010854: February 16, 2011 report written by Jurgen Trzewik and Christophe Vailhe titled "Biomechanical consideration for Pelvic floor mesh design
[16] ETH.MESH.03753245: PowerPoint presentation titled "Biomechanics (Pelvic Forces)"
[17] Christoph Vailhe Deposition June 20, 2013 45:23-46:11
[18] ETH.MESH.04005863: Yves Ozog, Theoretical and Experimental Evaluation of Implant Materials used in Pelvic Organ Prolapse Repair (Doctoral thesis in Medical Sciences 2001)
[19] ETH.MESH.07191144: Stepan Janda, Biomechanics of the pelvic floor musculature (Thesis)
[20] Vailhe deposition 06/21/2013 251:11 to 252:15

carried out by the likes of Cobb, Klosterhalfen and Klinge to name a few as it was assumed that they [were] primarily researching Inguinal Hernia repair and it didn't translate to Pelvic Floor. As it turns out, the vast majority of their work is pre-clinical which mirrors the more recent work done by Cosson, Boulanger, Rubod et al. done for the Pelvis."[21]

Mr. Meek's statement is actually only partly true. Yes, our work was to a large extent "pre-clinical" in order to better understand certain design parameters of hernia meshes. However, unfortunately, our work was not continued by Ethicon in its development of pelvic meshes in that they failed to define the physiological forces in the pelvis and thus to translate this to design consideration for pelvic meshes. The work by Cosson et al. is preliminary in this regard. As Ethicon's own documents point out, there are still many unknowns regarding how best to design pelvic floor meshes in light of the still undefined physiologic requirements of pelvic floor and in particular, vaginal tissues. As Mr. Meek points out later in his email, these studies from the late 1990's have a few key points. Two of these that he communicates to the sales force are that "PP is the best of a bad lot re integration and retraction and there is a need to develop grafts that mimic the human tissue mechanical properties… [and] the need for grafts with elastic properties to match [the hyperelastic properties of the vagina]."

Unfortunately, Mr. Meek was not the only Ethicon employee who was misguided in this analysis. In May 2007, while the Prolift +M team was recommending updates to the IFU, they also attempted to use our 1998 rat study to support claims in their IFU for Prolift +M. It was disingenuous, at best, and closer to misleading for Ethicon to use a ten-year-old hernia mesh study from the abdominal wall of rats to validate their claim that Prolift +M would "illicit a minimum to mild inflammatory reaction" and "thus incorporate the mesh into adjacent tissue."[4]

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They also used our study from 1998 to claim that "the bi-directional elastic property allows adaptation to various stresses encountered in the body." First of all, the mesh we used in our study was Vypro, which was a multifilament PP mesh designed for the abdominal wall. Additionally, Vypro's PP fibers were intertwined with an absorbable component, polyglactin-910. Finally, the mesh in our study was implanted in abdominal tissue, not pelvic tissue. This is quite different from the use of Prolift in the female pelvis.

In another unfortunate example of the internal confusion and disparity of knowledge regarding surgical mesh and specifically, the differences between the tissues of the abdomen versus the pelvis, is seen in an email by a top R&D scientist, Joerg Holste, when he stated in March 2007, "My thinking is that a pelvic floor prolapse is clinically comparable to hernia development, because it is part of the abdominal wall."[22]

Clearly, the scientific reality weighs in favor of Dr. Robinson's analysis much more so than Dr. Hoelste's. More recently, Dr. Daniel Elliott of the Mayo Clinical published an article stating two very obvious concerns that should have been raised: "The first concern this should have raised regarding using synthetic mesh in the vagina is that synthetic meshes are not a perfect solution for abdominal wall hernias. A tremendous amount of data in the general surgery

[21] ETH.MESH.02207388: Email dtd 10/26/08 from Jonathan Meek to Julie Bird et al regarding Prolift + M Pre-Reading

[22] ETH.00078537: Email dtd 03/07/07 from Joerg Holste regarding Lightning 510(k) requirements, "POP is part of the abdominal wall"

literature details a long litany of mesh complications…The second question or concern that should have been raised and thoroughly studied prior to widespread industry acceptance of transvaginal mesh kits is that the vagina is not the abdominal wall."[23]

I agree. I also agree with Ethicon's conclusions in its analysis just last year in 2011 regarding the biomechanical considerations for pelvic floor mesh design: "We have shown that currently there is an important need for animal models in pelvic floor research…Of course, we ultimately need to know what is happening in the human female…The development of knowledge to understand the mechanics of pelvic floor disorders is imperative; yet, we are only just beginning to determine the necessary criteria on which to base design for pelvic floor implants."[24] This admission by Ethicon comes 11 years after putting Gynemesh PS on the market and 6 years after putting Prolift on the market as a "revolutionary" procedure. From the time of the launch of Prolift in 2005 until the present, Ethicon continues to lack sufficient knowledge regarding pelvic floor in vivo forces and has never adequately calculated or estimated such forces through appropriate testing.[22] [25] [26]

Strength

Measurements of the tensile strength of human tissue indicate a maximum strength of about 20 N/cm before rupture. Estimates of maximum physiological abdominal wall tensile forces indicate a maximum of 16 N/cm for smaller defects and 32 N / cm for larger defects. These limitations should be provided in all directions and considered as the minimal limit of the force for subsequent tearing. Although testing of sufficient tensile strength in the pelvic floor has been understudied, one can assume that it would not exceed the tensile forces in the abdomen (16 N/cm).

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The Gynemesh PS white paper similarly states that strength is an important property of synthetic meshes. It also states that "Although in vivo forces and exerted strains on pelvic floor repairs are difficult to quantify, it is unlikely that they are significantly different than those found in the abdomen. Synthetic meshes have been used for years in the repair of abdominal and inguinal hernias and have proven to be of adequate strength to provide tissue support in that region. In fact, many meshes may be over-engineered with respect to strength and mesh density and weight may be able to be significantly decreased. However, the extent of this decrease and the minimum mesh strength requirement for pelvic floor repair is not known."[27] It is not possible to design an appropriate surgical mesh if the surgical environment is not understood.

Holste reported in 2005 in an article "Are Meshes with Lightweight Construction Strong Enough?" that surgical mesh must provide sufficient biological strength to meet physiological requirements without being over engineered. He added a graph to his publication showing that the maximum tensile strength on the abdominal wall is 150mmHg. The graph demonstrates that

[23] Elliott, D. CON: mesh in vaginal surgery: do the risks outweigh the benefits? Wolters Kluwer Health. 2012
[24] ETH.MESH.02010834-ETH.MESH.02010854: February 16, 2011 report written by Jurgen Trzewik and Christophe Vailhe titled "Biomechanical consideration for Pelvic floor mesh design"
[25] ETH.MES.01156032: Clinical Expert Report for Gynecare Prolift Pelvic Floor Repair System
[26] Christoph Vailhe deposition 45:23-46:11
[27] ETH.MESH.02053630: Gynemesh PS "White Paper"

Ethicon's hernia meshes Ultrapro, Prolene Soft and Prolene all have burst strengths that are far above the maximum needed strength in light of the maximum abdominal pressure (Ultrapro = 650 mmHg; Prolene Soft = 700 mmHg; Prolene = 1650 mmHg). Holste correctly notes that over-engineered meshes (i.e., those whose strength is far above the maximum requirements of the tissue in which it is implanted thus leaving excessive amounts of foreign material in the body) lead to stiffness, excessive scar plate formation and abdominal wall restriction, all of which in turn lead to complications of reduced patient comfort and chronic pain. However, in that same article, he states that these meshes "possess adequate strength to repair the abdominal wall." He has missed the point. The question is not whether the meshes have enough or adequate strength, the question for Holste and his employer, Ethicon, should have been (and continues to be even to this day) "Do our meshes have more material and/or more strength than is required to accomplish the task of reinforcing the tissues in which they are implanted?". His conclusions thus belie a proper analysis of the data that he seeks to present given that Prolene Soft is over four times stronger than the maximum tensile strength of the abdomen, and Prolene is over ten times the required strength. [28]

Again, the main task for reinforcement by textile structures is the compensation of any tensile strength. In the case of prolapse, it should retain the pelvic floor with its organs, which means there will be tension by definition. Thus, declarations or claims by Ethicon that the Prolift Kit are "tension free" are untrue and defy scientific sense or even common sense. The bearing of forces by the textile area is much more complex and hardly possible to be calculated exactly for every part of the mesh.

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However, as Cosson et al.[29] discovered, the vaginal tissue showed rupture at a strain of about 20 N/cm. Thus, any textile does not need to be stronger than this; however, more precise measurements or estimations are still lacking.

Ethicon has indicated in its internal documents that a force of 12.0 lbf (53 N) is placed on the mesh arms of the Prolift during implantation and that the required forces to pull the mesh arms through the cannula to be 0.73 lbf (3.24 N).[30] [31] It has also stated in other documents that the tensile strength of the implant straps "shall exceed 2.3 kg-force" (23 N).[32]

During the development of Project Thunder, it was noted by the design team that as of 2008, pelvic floor material was still over-engineered. "There is no patient-centric PF material!...we need less foreign body material and materials that correlate to measured female pelvic physiological characteristics"[33] Ethicon's researchers, when developing Project Thunder, they admitted that their own "pelvic floor materials are still over-engineered."[34] This would include the mesh in the Prolift.

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[28] ETH.MESH.02227224: PowerPoint Presentation dtd 05/09/08 titled MGPP Thunder Decision Meeting
[29] Cosson M, Lambaudie E, Boukerrou M, Lobry P, Crépin G, Ego A. A biomechanical study of the strength of vaginal tissues. Results on 16 post-menopausal patients presenting with genital prolapse. Eur J Obstet Gynecol Reprod Biol. 2003 Feb 10;112(2):201-5.
[30] ETH- 01754: FDA Letter stating necessary force for arm pull out
[31] ETH.MESH.00906445: Email dtd 01/18/08 from Vincenza Zaddem to Bryan Lisa regarding 510(k) mesh data with strength
[32] ETH.MESH.01992236: "Form for Test Method Applicability/Suitability"
[33] ETH.MESH.02227224: PowerPoint Presentation dtd 05/09/08 titled MGPP Thunder Decision Meeting
[34] ETH.MESH.01405170: PowerPoint Presentation dtd 6/18/07 by Cliff Volpe & Peter Meier title "Exploratory Program 'Thunder'"

Elasticity

As stated in their Gynemesh PS "White Paper", Ethicon knew the importance of a pelvic mesh that was stretchable in all directions due to the complex, dynamic, multi-axial, three dimensional nature of the pelvic region. "Designing a mesh …. First, it is important to consider rigidity / flexibility … [this is] extremely important when considering the dynamic nature of the tissues surrounding the vagina wall. An ideal mesh would be multi-directionally stretchable, easily conforming to tissues in the region of the repair. This would reduce the amount of tension on the fixation sutures allowing the tissue to function normally."[35]

Ethicon states that "Prolene Soft Mesh is knitted by a process which interlinks each fiber junction and which provides for elasticity in both directions. This construction permits the mesh to be cut into any desired shape or size without unraveling. The bi-directional elastic property allows adaptation to various stresses encountered in the body." [4]

After Ethicon obtained FDA 510(k) clearance for Prolene Soft, Ethicon used the "bi-directional elasticity" language in its IFU. In 2002, when FDA cleared Gynemesh PS, the same language appeared in its IFU. In July 2007, seven years after Prolene Soft was cleared for marketing, the FDA learned that Ethicon had been selling Prolift kits for two and a half years without proper clearance. In response to Ethicon's subsequent submissions to FDA in an effort to obtain 510(k) clearance to market both Prolift and Prolift +M, the FDA reviewer, Dr. Jiyoung Dang, questioned a number of Ethicon's claims including its claims of bidirectional elasticity and that this property allows adaptation to various stresses encountered in the body.

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Various Ethicon employees attempted to find any evidence they had to support these claims. Dr. Christophe Walther (Ethicon Germany) questioned what was meant by "bi-directional elastic properties" or "allows adaptation to physiological stresses" and asked who was responsible for these statements. Vincenza Zaddem (Ethicon Engineer and Team Leader of Prolift +M) stated "the team felt justified to use the statement 'bi-directional elasticity and that this property allows adaptation to various stresses encountered in the body' because this is the same statement used in the IFUs for PROLENE Soft Mesh and GYNEMESH PS. Since this is standard data collected for meshes, **without verifying we assumed we had data for UP demonstrating it is elastic in both directions."** (Emphasis added).[36] Apparently, Ethicon also "assumed" they had this data for the Prolift but, after searching, Ethicon employees were unable to find data to support their claims and thus, they informed FDA that they would withdraw this claim from the Prolift IFU.

Structural Stability with regard to Strength and Elasticity

The principle of "tension free" might be somewhat true for meshes places in the abdominal wall, but the textile structures in the pelvic floor necessarily, and by definition, cannot be "tension free". Their fixation to ligaments indicates that their function has to consider resistance

[35] ETH.MESH.02053630: Gynemesh PS "White Paper"
[36] .MESH.021989933: Email datd 9/10/07 from Christoph Walther to Vincenza Zaddem regarding "Info needed for FDA – Lightning", in which Zaddem states they "assumed they had data for UP".

against tearing stress and to prevent prolapse of the tissue under mechanical strain. Thus, any claim by Ethicon that their pelvic meshes are "tension free" is false and misleading.[37]

In general, the huge variety of the different settings for measuring stability, elasticity, or porosity that are applied by mesh manufacturers, hinders the direct comparison of the material properties. The elasticity is markedly less for Gynemesh PS Mesh®. During the manufacturing process, the mesh used in the Prolift kit is laser cut off of a large piece of Gynemesh PS. The edges of the Prolift mesh are still frayed leaving the end of the filaments "barbed" with irregular, sharp edges. At very low strain, the Prolift arms show a considerable rolling in, sometimes referred to in Ethicon documents as "mesh curling", "roping", or "lack of stress-shielding". Notably, even after relaxation of the arms after strain, the "curling" of the arms persists, indicating a plastic deformation of the structure. It is my opinion, to a reasonable degree of medical and scientific certainty that the frayed edges, "roping" and "curling" under minimal strain, excessive elasticity leading to pore deformation under strain, and lack of memory after strain of Gynemesh PS mesh, all are design failures that cause Prolift to have an unsafe design that unreasonably increases the risk of injury to patients in whom it is implanted. During testing that Ethicon performed in 2000, they claimed that at less than 2 pounds of force, Prolene Soft mesh does not curl.[38] I have determined in my work with Prof. Muehl that this is not the case. In fact, Ethicon Medical Affairs Director, Piet Hinoul listing mesh roping as a hazard for both mesh exposure and tissue damage in his 2013 Clinical Expert Report for Prolift +M.[39]

V. BIOCOMPATIBILITY

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Biocompatibility of long-term implantable medical devices can be defined as 'the ability of the device to perform its intended function, with the desired degree of incorporation in the host, without eliciting any undesirable local or systemic effects in that host'. More simply put, biocompatibility entails optimal cellular response and tissue ingrowth. Piet Hinoul, the Ethicon Medical Affairs Director, agrees in his deposition that it was important for Ethicon to develop a mesh construction that would ensure only the desired amount of fibrosis because "you would want to limit excessive fibrosis."[40]

Histopathological investigations have shown that the amount of fibrosis is directly related to the amount of the inflammatory, cellular foreign body reaction (FBR) induced at the biomaterial/host-tissue interface. This was the primary reason we directed out early mesh research to decreasing the surface area of the mesh materials in relation to the physiological biomechanical requirement to minimize the biomaterial/host-tissue interface area. This realization and design shift led to our development of what became known as "the lightweight, large pore concept" as detailed earlier in this report. The superiority of lightweight, large pore meshes over the classical heavyweight, small pore mesh materials (like Marlex and Prolene) is now widely accepted. These large pore or "macroporous" meshes, defined as pore sizes of >1mm in all directions, after accounting for stretch and pore deformation, have a decreased

[37] ETH.MESH.00086463: September 3, 2009 Email from Piet Hinoul Re: Prosima take away messages
[38] ETH.MESH.02613708: Completion Report Design Verification for Soft Prolene Mesh/Mesh Curling
[39] ETH.MESH.08315779 – Piet Hinoul 2012 Prolift +M Clinical Expert Report
[40] Piet Hinoul Deposition 540:1-10; 544:6-17; 545:5-13; 574:25-575:18

surface area, and compared to classical mesh materials, they induce a reduced inflammatory reaction with a decreased amount of clinical complications.

Weyhe et al. did a comparison study of heavyweight versus lightweight meshes to evaluate whether weight and structure of PP meshes were independent determinant factors for tissue incorporation of the implant. Their conclusion was that there can be worse biocompatibility of lightweight meshes compared with heavyweight meshes, if the lightweight mesh has very small pores. "Thus, the amount of implanted mesh was not the main independent determinant of biocompatibility (expressed as successful incorporation and diminished foreign body reaction) but the size of the pores."[41] As between "lightweight" or "large pore", large pore was considered by far the most important design construct for maximum biocompatibility and thus a potential deterrent to mesh-related complications.

Not surprisingly, attempts to objectify the weight parameters or values for the best "lightweight" design were inconclusive and/or varied. A review of the scientific literature indicates that there has been no real consensus as to the categorization or definition of the weight limits by class.[42,43,44,45,46,47,48] In numerous documents in which they communicated their mesh weight classification to FDA, surgeons and patients, Ethicon stated that Prolene Soft/Gynemesh PS/Prolift were "lightweight". However, according to Cobb and Weyhe, at least, Ethicon's PS mesh was "medium weight", whereas Vypro, Ultrapro and Prolift+M would be considered "lightweight". [49] [50] The deposition testimony of an Ethicon Key Opinion Leader employee also reveals Ethicon's lack of understanding as to what constitutes "lightweight". In 2008, Vince Lucente, a urogynecologist who was the number 1 promoter of Prolift and Prolift +M, referred to Gynemesh as a "middle weight mesh".[51]

Therefore, to try to overcome some of these inconsistencies and hurdles, and to try to provide valuable guidance to surgeons who are considering whether to implant a mesh and if so, which ones, we set out to create a new classification of hernia meshes. Rather than using weight as the defining parameter, we contacted major manufacturers of meshes in and collected the physicochemical data of their products with the goal of deriving a classification system that grouped meshes according to their biocompatibility.

As we stated in our published article[52], it is important to note that even if a hernia mesh is considered "large pore", based upon the above classification, in order to avoid "fibrotic

[41] Weyhe D, Schmitz I, Belyaev O, Grabs R, Muller K, Uhl W, Zumtobel V. Experimental Comparison of Monofile Light and Heavy Polypropylene Meshes: Less Weight Does not Mean Less Biological Response. World J Surg. 2006 Aug;30(8):1586-91
[42] ETH-47802: Cobb WS, Burns JM, Peindl RD, Carbonell AM, Matthews BD, Kercher KW, Heniford BT Textile analysis of heavyweight, mid-weight, and lightweight polypropylene mesh in a porcine ventral hernia model..J Surg Res. 2006 Nov;136 (1):1-7. Epub 2006 Sep 22.
[43] Cobb W, Kercher K, Heniford T. The Argument for Lightweight Polyropylene Mesh in Hernia Repair. Surgical Innovation. 2005; 12(1):T1-T7
[44] Weyhe D, Belyaev O, Buettner G, Mros K, Mueller C, Muerer K, Papapostolou G, Uhl W. In Vitro Comparison of Three Different Mesh Contructions. ANZ J. Surg. 2008; 78:55-60
[45] Deeken C, Abdo M, Frisella M, Matthews B. Physicomechanical evaluation of absorbable and nonabsorbable barrier composite meshes for laparoscopic ventral hernia repair. Surg Endosc. 2011; 25:1541-1552
[46] ETH.MESH.0081180: Prolift characteristics
[47] ETH.MEH.02212840: Mesh Structures chart
[48] ETH.MESH.02227368: Meshes/Devices Chart
[49] ETH.MESH.04037392: Prolift+M Sales Training Program PowerPoint Presentation
[50] Axel Arnaud Deposition: 375:3-376:6
[51] ETH.MESH.0067363: Vince Lucente webinar transcript
[52] Klinge U, Klosterhalfen B. Modified Classification of surgical meshes for hernia repair based on the analyses of 1000 explanted meshes. Hernia. 2012: 1-8

bridging" (discussed below), even large pore meshes must have a sufficient amount of "good pores" (>1mm in diameter, after stretch) in order to resist this consequence of the inflammatory process.

Foreign Body Reaction

All experimental and clinical studies indicate that mesh products on the market today cause an initial and chronic inflammatory tissue response in the recipient after implantation. The quality of the inflammatory reaction to foreign bodies of different natures is surprisingly constant, characterized by a rapid accumulation of huge numbers of phagocytic cells, in particular, blood monocytes and tissue-derived macrophages. This type of inflammatory process is known as a foreign body reaction (FBR). It is characterized by an initial inflammatory burst caused by a release of a huge cocktail of potent inflammatory mediators which then attract other cell types including T-cells, polymorphonuclear granulocytes (PMNs), plasma cells and fibrocytes. Within a few days, this cellular activity forms an early granuloma layer recognized by the very typical foreign body giant cells and an outer layer of fibrosis with deposition of collagen. This late stage granuloma is not a static type of chronic inflammation but rather, it represents a chronic wound with an increased cell turnover even years after implantation. Monocytes and tissue-derived macrophages, at the interface and in contact with the polymer, undergo apoptotic cell death and are replaced. [Fig. 6]

We published our results in 1998 and 1999 of the histological analyses from explanted mesh from rats, dogs and humans. The tissue response in humans was almost identical to the morphological observations in the animal models. In our 1999 study, we reviewed approximately 350 human explant samples of various mesh modifications gathered from centers all over Europe. Even 15 years after explantation, the longest observation in our study, a persistent chronic FBR could still be detected, indicating that mesh is likely never completely inert with respect to local inflammatory processes. The persistence of this FBR is important, especially in younger patients in whom the mesh will remain for several decades. The delay before explantation of mesh for infection of up to 56 months, for chronic pain of up to 48 months and for recurrence of up to 180 months established that in many clinical studies with shorter surveys of less than 1-2 years, the morbidity rates are underestimated.[53,54]

Fibrotic Reaction

PP filaments cause an intense inflammatory response in the abdominal wall as well as the tissues of the pelvic floor. There is increased fibrotic reaction which stimulates remodeling at the tissue/implant interface. This intense scar formation contributes to the wound contraction.[55]

Fibrotic Bridging

In our studies from the late 1990's, in which we evaluated the inflammatory response and fibrotic reaction in the tissues at the interface with the mesh implant, we saw that that large pore

[53] Klinge U, Klosterhalfen B, Muller M, Ottinger A, Schumpelick V. Shrinking of Polypropylene Mesh in vivo: An Experimental Study in Dogs. Eur J Surg. 1998: 164; 965-969
[54] Klinge U, Klosterhalfen B, Muller M, Schumpelick V. Foreign Body reaction to Meshes Used for the Repair of Abdominal Wall Hernias
[55] Steinau, G., U.Klinge, A.Tittel, H.Skopnik, V.Schumpelick (1992) Gallenblasensteine im Kindes- und Jugendalter. Akt. Chir. 27:267-9

mesh (Vypro) was integrated into a loose network of perifilamentous fibrosis with fat tissue present in between the fibers. In contrast, the small pore mesh was incorporated entirely in perifilamentary granulomas and scar tissue, which bridged the whole pore diameter <1 mm. This phenomenon, known as "fibrotic bridging", exists when granulomas, side by side, form a common outer fibrotic capsule joining each mesh fiber and forming a rigid "scar plate" covering the whole mesh. This scar plate leaves no space for further tissue ingrowth and leads to a number of complications including loss of elasticity and pain associated with the rigidity, shrinkage or contraction of the mesh, mesh erosion, nerve entrapment, bacterial encasement, chronic pain and dyspareunia, if used in pelvic floor repair.

With the development of Vypro, the first truly large pore mesh, we were able to increase the pore size by up to 500-600% (Vypro 3-5 mm vs. Prolene <1mm). Given that the risk of bridging fibrosis is increased by mesh with pore size < 1mm in all directions, any mesh designed with pores this small increases the risk of injury to the patient and is a less safe design than mesh with pore sizes > 1mm in all directions. Simply put: the greater the pore size or open space in between fibers, the less the risk of fibrotic bridging and formation of a rigid and potentially dangerous scar plate encapsulating the mesh. Ethicon had this information beginning in 1998.

Effective Porosity

In approximately 2005, I applied for and received a grant to study the porosity of textile meshes in an attempt to objectify porosity in a reproducible manner. I contacted an engineer at the FH Aachen University of Applied Sciences, Thomas Muehl, and we embarked on a two-year project to create a porosity image analysis system that better characterized the pore geometry of meshes, both before and after strain. The results of this granted project were published in 2007 in the Journal of Biomedical Materials Research Part B: Applied Biomaterials.[56]

Our research was based on my previous work from the late 1990's that pore sizes that prevent fibrotic bridging and will permit tissue ingrowth should exceed 1 mm between two PP filaments. As stated in our publication, "To exclude large pore areas that may be provided by long and thin pores with narrow parts of pores, the pore geometry has to be evaluated as well. Therefore, only those pores and those parts of the pores are extracted, which have dimensions greater than 1mm or 1000 μm in all directions. The remaining porosity is defined as 'effective porosity'.

In connection with this litigation, Prof. Muehl performed testing on Prolift and Prolift +M meshes using the same protocol as we used in our study in 2007 and we published these results in 2013.[57] [58] (NOTE: An Ethicon R&D Scientist, Vincenza Zaddem, Team Leader of Prolift +M and Technical Lead of Prolift, was shown the Muehl study from 2007 and she testified that it sounded like a valid test and that she believed that it would be a good test for Ethicon to look into in order to determine the effective porosity and effective porosity under strain of their pelvic

[56] Muehl T, Binnebosel M, Klinge U, Goedderz T. New Objective Measurement to Characterize the Porosity of Textile Implants. J Biomed Mater Res Part B: Appl Biomater. 2007; 84B:176-183
[57] Prof. Tomas Muehl Report
[58] J. Otto, et al., Elongation of textile pelvic floor implants under load is related to complete loss of effective porosity, thereby favoring incorporation of scar plates; J Biomed Mater Res A 2013 Apr 29

meshes.[59] This was again confirmed in sworn testimony by Ethicon employee, Joerg Holste and circulated numerous times within Ethicon as a "more sophisticated set up" than Ethicon's method of porosity testing. [60] [61] [62] Ethicon was also aware of the concept of "effective porosity" and the necessity of maintaining pore sizes of >1mm after stretch.[63] [64] [65])

The significance of the Muehl method of testing these mesh products is that it provides useful data in terms of how the mesh, and different parts of the mesh, will perform in the human body. The first most important observation from this testing was that the effective porosity and the effective porosity under strain in Prolift produced less than optimal results. As minimal strain was applied to the test sample, the geometric shape of the pores deformed and ultimately collapsed. This deformation led to extremely small pores which would make the mesh highly susceptible to fibrotic bridging, encapsulation by a rigid scar plate and the array of potential complications that occur as a result of this inflammatory process.

Another significant observation during the porosity testing by Prof. Muehl was the "curling", sometimes referred to as "roping", that occurred in the mesh arms of the Prolift under minimal strain. We published an article in 2007 [66] in which we showed the tissue reaction and fibrotic ingrowth of PP due to curling/roping of the mesh due to scar shrinkage after H&E staining. [Fig. 9] As strips of mesh begin to curl, they act similarly to small pore meshes in that the fibers become situated too close together enhancing the inflammatory response and leading to fibrotic bridging.

Yet another significant observation during the porosity testing by Prof. Muehl was the "fraying" at the edges of mesh which could be seen upon removal from the package but became markedly worse in the Prolift mesh sample at minimal strain. These frayed edges create an increased inflammatory process. When frayed edges occur in the curled arms, an even greater inflammatory process is created.

After being subjected to even minimal strain or tension, the arms in the Prolift not only curled, frayed and demonstrated deformation of the pores, they also failed to return to their original or near-original geometric shape and design. This phenomenon is known in material science as plastic deformation.

It is my opinion to a reasonable, to a reasonable degree of medical and scientific certainty that mesh device that is permanently implanted in human tissue and reacts to implantation and in vivo forces in the manner in which the Ethicon meshes performed during Prof. Muehl's testing increases the risk of injury to patients in which it is implanted and is a less safe design than products that better withstand these in vivo conditions and do not display these poor outcomes as these material design properties cause increased inflammation, scarring, contraction, nerve

[59] Vincenza Zaddem Deposition Testimony 387:14-20
[60] Jorg Holste Deposition 417:9-418:22
[61] ETH.MESH.02184130 2008 email circulating New Objective to Characterize the Porosity of Textile Implants
[62] ETH.MESH.04945136 2010 email circulating New Objective to Characterize the Porosity of Textile Implants
[63] ETH.MESH.03021946 T-Pro Stage Gate Meeting on August 25, 2008
[64] ETH.MESH.02587926: When the Implant Worries the Body
[65] ETH.MESH.017525352: Mesh Design Argumentation Issues
[66] Klinge U, Binneboesel M, Kuschel S, Scheussler B. Demands and properties of alloplastic implants for the treatment of stress urinary incontinence. Expert Rev. Med. Devices. 2007; 4(3):349-359

entrapment, pain and the host of other complications outline herein. The PVDF product, Dynamesh, is a safer design than Gynemesh PS for all of the reasons stated above as further established in Muehl's testing.

Mesh Contraction

Mesh contraction, also known as mesh shrinkage, retraction, bunching or wrinkling is a common phenomenon after mesh implantation which is closely related to fibrotic bridging. [Fig. 15] Mesh contraction can be defined by a reduction of the surface area of the original implanted mesh. The surface reduction is due not to shrinkage of the mesh fibers themselves but rather to a retraction of the fibrotic scar tissues around the mesh. Retraction of the scar is a physiologic reaction of maturing scar which is characterized by a constant water loss and, consequently, a subsequent surface area decrease to an average of 60% of the former wound region. It is known to take place in the first few weeks after implantation but can last as long as 12 months or more after surgery. The medical literature and Ethicon's own internal documents report that there is considerable mesh contraction of surgical meshes made of polypropylene. [67,68,69,70,71,72,73] In fact, the TVM group in 2006 advised Ethicon of the common occurance of retraction or shrinkage in the Prolift arms and in the distal portion of the mesh which then creates a "cord-like" mesh.[74] This issue not only leads to poor coverage leading to recurrence, but will also increase the amount of foreign body reaction due to pore collapse. This phenomenon then leads to additional complications including: pain, dyspareunia, nerve entrapment, increased inflammation, urinary and fecal incontinence, urinary retention, blood vessel injury and others.

In February of 2007, Dr. Kerstin Spychaj, Ethicon R&D prepared a presentation entitled, "State of the knowledge in 'mesh shrinkage' – What do we know?" which she presented at an Ethicon Expert Meeting on February 23, 2007 at Ethicon's Norderstedt facility. Dr. Spychaj did a literature review and concluded that the "ideal mesh" in order to avoid shrinkage would be a lightweight material (partially absorbable) with a pore size > 1mm and mild but not excessive FBR and wound contraction with swift and adequate tissue growth.[75] Not only had Ethicon determined that shrinkage was obviously critical to the quality of its mesh products, they acknowledged it could cause "vaginal anatomic distortion which may eventually have a negative impact on sexual function." Furthermore, they stated that "its treatment is difficult."[76] Several

[67] ETH-47802: Cobb WS, Burns JM, Peindl RD, Carbonell AM, Matthews BD, Kercher KW, Heniford BT Textile analysis of heavyweight, mid-weight, and lightweight polypropylene mesh in a porcine ventral hernia model..J Surg Res. 2006 Nov;136(1):1-7. Epub 2006 Sep 22.
[68] Cobb W, Kercher K, Heniford T. The Argument for Lightweight Polyropylene Mesh iHernia Repair. Surgical Innovation. 2005; 12(1):T1-T7
[69] Cobb W, Kercher K, Heniford T. The Argument for Lightweight Polyropylene Mesh in Hernia Repair. Surgical Innovation. 2005; 12(1):T1-T7
[70] Tunn R, Picot A, Marschke J, Gauruder-Burmester A, Sonomorphological evaluation of polypropylene mesh implants after vaginal mesh repair in women with cystocele or rectocele. Ultrasound Obstet Gynecol. 2007 Apr;29(4):449-52.
[71] ETH.MESH.01192895: Velemir L, Amblard J, Fatton B, Savary D, Jacquetin B, Transvaginal mesh repair of anterior and posterior vaginal wall prolapse: a clinical and ultrasonographic study. Ultrasound Obstet Gynecol (2010)
[72] Letouzey V, Fritel X, Pierre F, Courtieu C, Marès P, de Tayrac R. Informing a patient about surgical treatment for pelvic organ prolapse. Gynecol Obstet Fertil. 2010 Apr;38(4):255-60.
[73] Vollebregt A, Troelstra A, van der Vaart C. Bacterial Colonisation of collagen-coated polypropylene vaginal mesh: Are additional intraoperative sterility procedures useful? Int Urogynecol J. 2009; 20:1345-1351
[74] ETH.MESH.01774758: December 2006 email regarding TVM Group mesh design input
[75] ETH.MESH.01218361-01218367: Dr. Kerstin Spychaj, State of the knowledge in "mesh shrinkage" – What do we know? 04/05/2007
[76] ETH.MESH.02992139: Lightning Clinical Strategy dtd 11/22/06

other Ethicon employees and/pr consultants provided sworn testify regarding the issue of mesh shrinkage.[77,78,79,80]

There is an email exchange date July 2004 regarding mesh contraction/shrinkage in which Axel Arnaud suggested adding "mesh shrinkage" as an additional adverse reaction in the Prolift IFU. Mesh shrinkage had not been included in the Gynemesh PS IFU. Sean O'Bryan, Ethicon Regulatory Affairs, stated that "If mesh shrinkage is a real issue, then we have an obligation to put it in." However, he also stated that if this new adverse reaction was added, Ethicon would also have to add it to the existing Gynemesh PS IFU as a modification.[81] Neither mesh shrinkage nor mesh contraction was added to the original or the revised Prolift IFU, nor was it added to the Prolift+M IFU.

Degradation

Studies, as early as the 1970's and 1980's, have demonstrated concern over the degradation/oxidation effects of polypropylene when used in the human body.[82,83] It was presumably due to such concerns that Ethicon adds anti-oxidative additives to its compound batches when formulating and extruding the PP resin – a process that has barely been revisited, retested or changed since the late 1960's.[84]

More recently, there has been growing concern regarding the degradation of PP in prosthetic mesh implants. It is believed that oxidation of the mesh occurs as a result of the chemical structure of PP and the physiological conditions to which it is subjected. This leads to embrittlement of the material, impaired tissue mobility and eventually chronic pain. Costello, et al. reported in 2007 that certain by-products of the inflammatory process cause the PP to be more susceptible to the oxidative effects of the metabolites produced by phagocytic cells during the inflammatory response. They saw cracks and other surface degradations such as peeling of the PP fibers under Scanning Electron Microscopy (SEM). [85]

Studies have demonstrated that PP is not biologically inert. Clave, et al. performed a comparative analysis of 100 pelvic mesh explants. The average period of removal was 790.6 days. Over 20% showed such degradation damage to the fibers. [Fig. 3] The article states that the

[77] David Robinson testimony 260:5-22
[78] Scott Ciarrocca testimony 2012-03-29 00, (Page 340:9 to 340:12)
[79] Aaron Kirkemo testimony 105:14-108:16
[80] ETH.MESH.03924887: Meshes in Pelvic Floor Repair
[81] ETH.MESH.02286052: Email dtd 1/13/05 from Sean O'Bryan to Scott Ciarrocca Re: IFU Prolift
[82] Liebert T, Chartoff R, Costgrove S. Subcutaneous Implants of Polypropylene Filaments. J.Biomed. Mater. Res. 1976; 10:939-951
[83] Williams D. Review Biodegradation of surgical polymers. Journal of Materials Science. 1982; 17:1233-1246
[84] ETH.MESH.0228619: Prolene Resin Manufacturing Specifications; Mary C, Maroid Y, King M. Comparison of the in vivo behavior of polyvinylidenflouride and polypropylene sutures in vascular surgery. ASAIO J. 1998; 44: 199-206; Wood, et al. Materials Characterization and histological analysis of explanted polypropylene, PTFE, and PET hernia meshes from an individual patient. J Mater Sci: Mater med (2013) 24:1113-1122; Costello C, Bachman S, Grant S, Cleveland D, Loy T, Ramshaw B. Characterization of Heavyweight and Lightweight Polypropylene Prosthetic Mesh Explants from a Single Patient. Surgical Innovation. 2007; 14(3):168-176
[85] Costello C, Bachman S, Grant S, Cleveland D, Loy T, Ramshaw B. Characterization of Heavyweight and Lightweight Polypropylene Prosthetic Mesh Explants from a Single Patient. Surgical Innovation. 2007; 14(3):168-176

lead author of the study had an educational position for Ethicon Europe.[86] Other authors have also written about the degradative effects of PP in the human body.[87,88]

The entire universe of clinical implications of a degraded, oxidized surface of PP mesh fibers in human tissue is not completely known. Such degradation, depending upon the severity, can lead to cracking and peeling of the fiber's surface creating an enhanced inflammatory tissue response due to the lack of a smooth surface coming into contact with the tissue. The mesh is not at rest after implantation. As a result of the inherent nature of the physiological forces and stresses being placed on the prosthetic after implantation, the mesh will move and stretch in an anisotropic manner in the tissue. This frayed surface can damage the tissue in which it is implanted leading to an increased host defense response at the tissue/implant interface.

Furthermore, the cracked and frayed fiber increases the surface area of the mesh. Increased surface area causes a more intense foreign body reaction and thus, a greater inflammatory/fibrotic response. Finally, bacteria are more likely to lodge in the cracked areas of the fiber surface in vivo thereby increasing the risk of infection which would also create a greater host defense response.

It is important to note that Ethicon hired an outside consulting firm, PA Consulting Group, to analyze its surgical mesh for the pelvic floor. In an extensive report, dated May 18, 2011, PA Consulting opined that "Polypropylene can suffer from degradation following implant….a process which initiates after a few days post implantation in animal studies."

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Numerous reasons are listed as possible causes of such degradation. In fact, one of the clinicians that PA Consulting interviewed when collecting data for the report "proposed that variability in the raw materials, and/or processing thereof, could be affecting the clinical performance and outcomes. He articulated his intention to investigate this hypothesis." A collection of "high resolution images of excised meshes clearly show physical degradation of polypropylene filaments." The report states that these images were collected from Prof. Klosterhalfen, but rather than include them in the report, PA Consulting says that the images are "on file".[89] These images of degraded Prolene mesh have been presented in numerous slide presentations around the world by Professor Klosterhalfen over the years.[90]

Degradation of PP in the human body has been the subject of scientific journals for decades, including one of which was authored by an Ethicon consultant, and at least one internal study. Yet Ethicon claims to the FDA, surgeons and patients that the PP material in Gynemesh PS and thus, Prolift is not "subject to degradation or weakening by the action of tissue enzymes." Internal documents reveal that there was some recognition of not only the degradative effects of

[86] Clavé A, Yahi H, Hammou JC, Montanari S, Gounon P, Clavé H., Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants. J Biomed Mater Res B Appl Biomater. 2007 Oct;83(1):44-9
[87] Cozad MJ, Grant DA, Bachman SL, Grant DN, Ramshaw BJ, Grant SA. Materials characterization of explanted polypropylene, polyethylene terephthalate, and expanded polytetrafluoroethylene composites: spectral and thermal analysis
[88] Ostergard, D. Degradation, infection and heat effects of polypropylene mesh for pelvic implantation: what was known and when it was known. Int Urogynecol J. 2011; 22:771-774
[89] ETH.MESH.02589032: May 18, 2011 report titled "Investigating Mesh Erosion in Pelvic Floor Repair" completed by Johnson & Johnson's PA Consulting Group
[90] What can we learn from explanted meshes? B. Klosterhalfen presentation Cologne, Saturday 8th of December 2012.

PP in surgical mesh but also that Ethicon's PVDF mesh, Pronova, was more elastic and demonstrated less degradation than PP.[91]

Interestingly, in the May 2013 deposition of Daniel F. Burkley, MS, 'principal scientist' in Ethicon's analytical characterization department, Mr. Burkley testified that in his 34 years at Ethicon, he was "…only familiar with one study ever conducted by Ethicon regarding possible degradation of its polypropylene sutures or mesh. This was a dog study that involved Prolene suture and at least two other competitors and perhaps another suture…[that he believed] was started around 1985." [and] "…I believe it was a cardiac [study].[92] The seven-year dog study demonstrates that the Prolene suture showed degradation of the Prolene suture that was still progressing after seven years, whereas the PVDF suture showed no such degradation. [93]

In my opinion, it has been proven to a reasonable degree of scientific certainty that surgical mesh made of PP and used in the pelvic tissues is not biologically inert and does in fact undergo degradation at the surface of the mesh fiber leading to an increased host inflammatory response. Therefore, Ethicon had a duty to test the potential degradative effects of the body's reaction to the PP mesh used in Prolift in order to determine whether the anti-oxidants that it has been using for some decades does, in fact, prevent surface cracking and peeling of the mesh fibers in the human tissue. According to their outside consulting group, they do not.

In my opinion, to a reasonable degree of scientific and medical certainty, it was inappropriate, false and misleading for Ethicon to claim that their PP meshes were not subject to degradation. In fact, Piet Hinoul, Ethicon's WW Medical Director, in a 2009 presentation stated that "[modern day meshes] are not biologically inert".[94] Furthermore, analyses of human explanted Ethicon meshes performed internally by Ethicon scientists, independently in the scientific literature and in relation to this litigation by pathology and polymer science experts, all prove, to a reasonable degree of medical and scientific certainty, that Ethicon's surgical meshes degrade in human tissue.[95]

Fraying/Particle Loss

In 2000, surgeons advised Brigitte Hellhammer, an Ethicon employee, that Gynemesh surgical mesh "released particles that migrate through the vaginal wall causing pain during intercourse".[96] In November of 2003, Marty Weisberg, who at the time was the Senior Medical Director of Gynecare, made a note to the TVT file indicating that there had been 58 complaints of mesh fraying since 2000.[97] In that memo to file, he stated that "Fraying is inherent in the

[91] C. Töns, B. Klosterhalfen, U. Klinge, C.J.Kirkpatrick, C. Mittermayer, V. Schumpelick (1993) Septischer Schock und multiples Organversagen in der chirurgischen Intensivmedizin. Langenbecks Arch Chir 378: 217-232
[92] In the United States District Court for The Southern District of West Virginia Charleston Division; In Re: Ethicon, Inc. : MDL No. 2327 Pelvic Repair System, Products Liability Litigation and Various Other Cross-Noticed Actions; May 22, 2013 30(B)(6) Deposition of Daniel F. Burkley, MS; pp 23 - 24.
[93] Daniel Burkley Deposition May 23, 2013 315:8-13; ETH.MESH.09557798
[94] ETH.MESH.01264260: Piet Hinoul 2009 Presentation
[95] Expert Reports of Vladimir Iakovlev & Howard Jordi; ETH.MESH.12831361; ETH.MESH.012831361; ETH.MESH.12831362; ETH.MESH.12831363; ETH.MESH.12831365; ETH.MESH.12831366; ETH.MESH.12831367; ETH.MESH.12831368; ETH.MESH.12831369; ETH.MESH.12831370; ETH.MESH.12831371; ETH.MESH.12831372; ETH.MESH.12831373; ETH.MESH.12831374; ETH.MESH.12831375; ETH.MESH.12831377; ETH.MESH.12831378; ETH.MESH.12831380; ETH.MESH.12831381; ETH.MESH.12831382; ETH.MESH.12831383; ETH.MESH.12831391; ETH.MESH.12831405; ETH.MESH.12831407
[96] ETH.MESH.03924887: Meshes in Pelvic Floor Repair
[97] ETH.MESH.00541379: Memo to File dtd 11/18/03 from Martin Weisberg Re: Mesh Fraying for TVT Devices

design and construction of the product. The mesh elongates in places; the mesh narrows in places; and small particles of Prolene might break off." Ethicon deemed elimination of particle loss as an important 'CTQ' (Critical to Quality).[98]

In November of 2003, Marty Weisberg, who at the time was the Senior Medical Director of Gynecare, made a note to the TVT file indicating that there had been 58 complaints of mesh fraying since 2000.[99] In that memo to file, he stated "Fraying is inherent in the design and construction of the product. The mesh elongates in places; the mesh narrows in places; and small particles of Prolene might break off." He also stated that the "stretching of the mesh increases the probability of fraying."

In 2003, Pariente published a study in which he evaluated the amount of material shed by different suburethral slings under certain test conditions.[100] Dr. Pariente's conclusion was that "the very high particle shedding for both Sparc (AMS) and TVT (Ethicon) may be of significant long term clinical concern in some quarters." TVT had the highest percentage loss of initial weight at 8.5%. Other authors have commented on the fraying phenomenon of Ethicon's TVT slings as well.[101]

The Pariente article then prompted the French regulatory agency, AFNOR to seek additional information from Ethicon regarding the high amount of particle loss. Ethicon Senior Scientist, Gene Kammerer believed that the method that AFNOR was requesting that they use in order to determine particle loss was unrealistic and too rigorous.[102] Kammerer, who apparently is not a medical doctor, also stated that particle loss "is most likely an aesthetic issue".[103] However, information regarding the impact of particle loss on foreign body reaction and its clinical outcomes is concerning and required further study by Ethicon. These particles cause a greater risk for bacterial adherence[104] and increase the area of inflammatory response surrounding the implant in the tissues. It is, therefore, inaccurate for this Ethicon scientist to simply state that there is no impact on clinical outcome of this loss of particles without clinical testing. Ethicon's Medical Director, Dr. Martin Weisberg, confirmed in his deposition that he was not sure whether or not particle loss and fraying would lead to clinical implications and did not know if Ethicon ever tested particulates for clinical implications.[105] One such implication was a report to Ethicon by a surgeon whose patient had erosion into her vaginal wall following implantation with a TVT sling.[106] The patient's husband reported that during sexual intercourse the "tape appeared frayed and tiny fibers were protruding through the vaginal wall".

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In 2004, Ethicon received clinical reports from other surgeons who were using their TVT products of this "crumbling" mesh problem. One of their key opinion leaders ("KOL's")

[98] 135. ETH.MESH.00301741: Email from Dan Lamont to Jacqueline Flatow dtd 11/21/05 Re:!!!!!GREAT NEWS FOR TVT LASER CUT MESH!!!!!
[99] ETH.MESH.00541379 Memo to File dtd 11/18/03 from Martin Weisberg Re: Mesh Fraying for TVT Devices
[100] ETH.MESH.01221055: Pariente J-L; An independent biomechanical evaluation of commercially available suburethral slings. Issues in Women's Health
[101] Moalli P, Papas N, Menefee S, Albo M, Meyn L, Abramowitch D; Tensile properties of five commonly used mid-urethral slings relative to TVT. Int Urogynecol J (2008) 19:655-663
[102] ETH.MESH.00583446 5/4/06 email from Gene Kammerer re French Regulatory and Particle Loss
[103] ETH.MESH.0058448 email re Urethral Sling particle loss standards and AFNOR
[104] Jongebloed WL. Doc Ophth 1986; 64:143, Sternschuss G. J Urol 2012; May 12 epub, Clave A. Int Urogyn J 2010; 21:261
[105] Weisberg deposition 5/31/13, 469:23 to 470:16
[106] ETH.MESH.02622276 TVT Complaint

informed the company that "it is embarrassing to see how the tape is crumbling" and it "gets worse if there is a stretch on the tape". This KOL for Ethicon, Dr. Eberhard stated "the quality of the tape is terrible" and "I can't understand that no one will solve the problem for such a long time". [107, 108]

While Ethicon employees such as Gene Kammerer believed this fraying and particle loss to be "an aesthetic issue", actual surgeons, including Ethicon KOL's, obviously believed differently. However, Ethicon chose to continue to sell their TVT mesh as it was with no design changes to address the problem. Instead, members of the sales and marketing team at Ethicon were instructed to tell doctors that "Prolene is proven to be inert"; that "the particles will not cause any problem"; and that the sales representatives should be "proactive" because "the competition will try to target this!"[109] Ethicon's position during this time was that the particles were not reactive and created no risk to patient safety.[110]

The 2006 Clinical Expert Report for TVT LCM indicated that LCM had decreased particle loss from MCM and that this "decrease would lead to less non-functioning material left in the tissues". [111] However, a *decrease* in excess polypropylene fibers loosening and separating from the mesh material does not indicate that the problem had been eliminated or appropriately mitigated. There simply is no patient benefit to excess, "non-functioning" polypropylene in a woman's pelvic tissues. More fibers migrating in the tissues create an additional foreign body reaction and inflammatory response at the site of each piece of mesh fiber in the body.

Despite the perceived advantage of decreased fraying and particle loss with its LCM, Ethicon still has the significant problem of a stiffer, more rigid mesh with LCM. In elongation studies conducted by Ethicon in 2004 comparing its MCM and LCM meshes to competitor meshes, Ethicon used an Instron machine (using uniaxial forces) to stretch the meshes to 20% elongation.[112] "At 1" of stretch, the laser-cut TVT mesh was about three times stiffer than the machine-cut TVT mesh…" The conclusion in this study focused not on the potential patient complications relative to this three-fold increase in stiffness of the LCM meshes, rather, Ethicon scientists concluded that "[c]utting the TVT mesh with a laser rather than a machine does not impact the established relationship between TVT and its competitors with regard to tensile behavior at low (20%) elongation."

In 2006, Gene Kammerer performed comparisons of LCM to MCM.[113] He placed samples of LCM and MCM mesh under strain to 50% elongation and found that the MCM samples showed "degradation of the structure of the mesh in certain areas where, because of particle loss, the knit has opened and a portion of the construction has been lost. The area may also be stretched and narrowed resulting in roping due to this occurrence." The LCM sample also showed stretching and narrowing, "but is generally less than the MCM".

[107] ETH.MESH.02180833 Translation of Eberhard Letter
[108] ETH.MESH.02180828 Eberhard complaint
[109] ETH.MESH.00865322 email from Charlotte Owens re Reminder on Blue Mesh!
[110] ETH.MESH.03535750 Letter to Herve Fournier re TVT Device, Blue Mesh; ETH.MESH.00541379 Memo re Mesh Fraying to TVT Devices; ETH.MESH.00858252: Memo re Mechanical Cut vs. Laser Cut Mesh Rationale
[111] ETH.MESH.00167109 Martin Weisberg Clinical Expert Report: Laser Cut Mesh for TVT
[112] ETH.MESH.01809080 Comparison of Laser-Cut and Machine-Cut TVT Mesh to Meshes from Competitive Devices (BE-2004-1641)
[113] ETH.MESH.08334244 email from Gene Kammerer re Photographs of LCM vs. MCM; ETH.MESH.00584811

The roping referenced in this Ethicon study, sometimes known as "curling", was seen at low force application in all of the mesh testing of Ethicon's Prolift, Prolift+M, TVT LCM and TVT MCM meshes that I have tested with Prof Muehl.

Ethicon Medical Affairs director, David Robinson, admitted at his deposition that the stiffer LCM was intended to address the roping problem. He testified that "customers were expressing they wanted a change with the particle loss, roping, change in tension during sheath removal" and admitted that one of the goals of LCM was to prevent roping and that roping was due to the elasticity problem with MCM.[114]

Based on these results and all of the Ethicon documents referenced above, it is hard to imagine how Ethicon could continue to sell and promote its TVT and Prolift products without some significant design change to the edges of the Prolene and Gynemesh PS mesh in its TVT and Prolift products. In an internal Ethicon email dated May 6, 2005, Ethicon Product Director, Allison London Brown, stated "[t]he basic story here is that the current mesh (MCM) is perceived by some physicians as inferior and we do get a high number of complaints on linting [fraying][115] and roping (mesh particles falling off and the material stretching to the point of being a string). The new material will dramatically reduce the incident of linting [fraying] and should all but eliminate the roping as it stays nice and flat". [116] Ms. Brown asked for her Ethicon colleagues to help her "craft" a story for its TVT customers (surgeons) to "reduce confusion and complexity" and to "tell a nice story without overly admitting that the current procedure may some have perceived aesthetic problems (not clinically relevant problems)."

In other internal Ethicon emails, Dan Smith from R&D explains that the TVT and TVT-O meshes cause more urinary retention than its TVT-Secur product because the TVT and TVT-O products "curl and rope which reduces the surface area of the mesh under the urethra and therefore, increases the pressure in a localized point". [117] At the deposition of yet another Ethicon employee, Dan Lamont, he confirmed Mr. Smith's statements saying "[t]here is a potential for roping to occur on the TVT mechanically cut mesh" but "Ethicon chose to continue to sell mechanically cut mesh".[118] An Ethicon TVT implantation DVD confirms Mr. Lamont's observations that even during the implant procedure; one can see the deformed pores and narrowing of the sling above the scissors and below the urethra while tensioning the sling intra-operatively. [119] Importantly, the top complaint of TVT surgeons from 2003-2006 was "Mesh Fraying/Roping".[120]

The TVT mesh is a knitted textile design without a sealed border and therefore, it has frayed edges that tend to shed particles of polypropylene before, during and after the surgery. As tension is placed on the mesh, it curls, ropes and sheds these particles, all of which make both

[114] Robinson deposition 07/25/2013 492:10 to 493:19
[115] Robinson deposition 07/25/2013 502:21-503:1
[116] ETH.MESH.00526473 Email from Allison London Brown re Laser-Cut mesh
[117] ETH.MESH.01822361 Email from Dan Smith re TVT Secur
[118] Lamont deposition 09/11/2013 25:8 to 25:20; 35:19-36:4
[119] ETH.MESH.PM.000004 TVT Retropubic Implantation Video
[120] ETH.MESH.00302390 TVT-Base & TVT-O Review for Laser Cut Mesh (LCM) Risk Analysis

TVT Mechanical-cut mesh (MCM) and TVT Laser-cut mesh (LCM) unsafe for their intended purpose of being permanently implanted in a woman's pelvic tissues. The frayed edges and the lost, migrating particles of both TVT MCM and TVT LCM as well as the increased stiffness and rigidity of TVT LCM can all lead to increased inflammatory response, chronic foreign body reaction, erosions, chronic pelvic pain, failure of the implant, dyspareunia, organ damage, urinary dysfunction and the need for surgical intervention. This same phenomenon of curled and roped mesh is evident in the Prolift implantation videos that I have been provided. To a reasonable degree of medical and scientific certainty, Ethicon failed to act as a reasonable mesh manufacturer by failing to properly design its POP and SUI mesh to avoid fraying, particle loss, curling and roping.

A reasonable mesh manufacturer should be less concerned about how its mesh design compares to its competition, and less concerned about telling a "nice story" to physicians to justify selling "inferior" meshes and more concerned with how its product affects the patients in which it will be permanently implanted. Neither Ethicon's MCM nor its LCM meshes are safe for their intended purpose of being permanently implanted in a woman's pelvic tissues. The frayed edges and the lost, migrating particles as well as the stiffer, more rigid mesh can both lead to increased inflammatory response, chronic foreign body reaction, erosions, chronic pelvic pain, failure of the implant, dyspareunia and the need for surgical intervention.

More probably than not, particulates of this nature will create a host defense response that includes the same series of cellular reactions as the main portion of the mesh. Also, more probably than not, particulates scattered throughout the pelvic tissue will create an inflammatory response of some magnitude; will increase the overall foreign body reaction and inflammatory response; will increase the amount of the fibrotic reaction; and will run the risk of migrating into other parts of the body. A simple, reasonable and safer alternative mesh design to have reduced, if not eliminated, the fraying would have been a border or seam at the edges of the Prolift and TVT mesh. This border would also reduce, if not eliminate, mesh curling and roping. Unfortunately, I have seen no documents or deposition testimony to indicate that Ethicon ever performed design testing to address these critical issues.

In addition to the Dynamesh products, there are a number of other meshes made with sealed borders that are on the market and sold in the U.S. The technology of weaving a seam or a sealed border on textiles has been available for many, many decades and therefore, such technology existed before woven polypropylene surgical meshes for the pelvic tissue (i.e., slings and POP mesh) were sold on the market beginning in 1997. As such, and to a reasonable degree of medical and scientific certainty, the open, unsealed borders of Gynemesh PS, unnecessarily increase the risk of patient complications and injuries. There were and are safer alternative mesh designs to Gynemesh PS that would have eliminated and/or drastically reduced this risk.[121]

VI. CLINICAL OUTCOMES/COMPLICATIONS

Poor design leads to poor outcomes. Failure of a mesh manufacturer to properly and thoroughly identify and consider the relationship between the risk of complications and its

[121] Trial testimony taken 11/10/14 and 10/04/15

relationship to design characteristics can have drastic, dangerous and life-changing consequences for patients. Neither surgeons nor patients are charged with the responsibility of designing and testing surgical meshes in a safe manner or being apprised of the latest scientific knowledge regarding the relationship between reported complications and their relationship to potential product design defects; this burden and responsibility falls squarely, and justifiably, on the shoulders of the manufacturer. Likewise, it is the responsibility of the manufacturer, not the physician or the patient, to appropriately warn of the known or knowable safety risks that accompany a particular product.

When asked about complications related to Ethicon's pelvic meshes, Ethicon former Director of Medical Affairs, Dr. David Robinson testified at his deposition in this matter as follows: "So what we have to do is assure that our product, per se, meets the characteristics that we are describing it having."[122] If designing a safer pelvic mesh product was not possible, Ethicon had an obligation not to market the product. Had Ethicon acted safely and reasonably with regard to its design, manufacture and sale of its pelvic floor mesh products, Prolift would have never been on the market for seven years and serious harm and injury to patients could have been avoided.

Another Ethicon Medical Affairs Director, Piet Hinoul, testified that Ethicon knew of all of the complications BEFORE Prolift was launched: [123]

- Mesh exposure that is difficult to treat and requires multiple operations;
- Serious complications with a significant effect on the quality of life for the patient;
- Narrowing of the vaginal wall;
- Significantly scarred vagina;
- Life-long risk of erosions;
- Retractions that could lead to recurrence of prolapse, postoperative pain and dyspareunia;
- Prolonged or Permanent inability to void their bladder;
- Every reoperation is considered an adverse event;
- Vaginal rigidity in the context of mesh retraction;
- Potential cause of recurrence cause by individual anatomical variation;
- Complex mesh erosion;
- Chronic pelvic pain syndrome;
- Life-changing symptoms despite multiple interventions to treat Prolift complications;
- Possible inability to achieve complete symptom resolution;
- Mesh contraction can be difficult or impossible to treat;
- Mesh contraction can cause severe pain that may never resolve despite conservative and surgical treatment;
- In the event of mesh related complications, it may be difficult to safely and effectively remove the mesh;
- Some patients will have a severe inflammatory reaction to the mesh, which will be chronic;

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[122] David Robinson Testimony 199:9-200:2
[123] Hinoul trial testimony *Gross,et al. vs Gynecare, et al* 01/16/13:1151:5-1156:14; 1087:1-17; 1058:22-1059:3

- The inflammatory reaction to the mesh will, in some women, result in the formation of scar plating/bridging fibrosis across the mesh. This increased the risk of complications;
- Some patients will suffer complications that will make it impossible for them to have comfortable sexual relations for the rest of their lives;

In his Clinical Expert Report supplement of August, 2012, Dr. Hinoul listed the multiple "harms and hazards" of Prolift +M that he said were known before both Prolift and Prolift +M went on the market to be permanently implanted in women.[124]

The medical literature is replete with peer-reviewed reports documenting complications with surgical mesh for pelvic organ prolapse and stress urinary incontinence.[125,126,127,128,129,130,131,132,133]

In addition, there have been 'Ethicon Expert Meetings' during which the issue of serious patient complications, were discussed.[134,135] I reviewed an Ethicon document entitled "WW Customer Complaints" from March 16, 2005 to July 10, 2008.[136] In the WW Customer Complaints document a total of 231 complaints were recorded as being received on Prolift, 145 of these reported as "Serious Injury". The top complaints were: mesh exposure (14%); erosion (12%); pain (12%); bladder perforation (9%); dyspareunia (5%); bleeding (5%); recurrence (5%). Because Ethicon acknowledged that "It is obvious that in most cases the terms **'exposure', 'erosion', and 'extrusion'** are used interchangeably", the mesh **erosion** rate could be as high as 26% from this reporting.[137]

Ethicon used Prof. Klosterhalfen as an outside pathology consultant to do histological evaluations at the Duren Institute of Technology of explanted mesh samples received by Ethicon. As of April 2008, he had analyzed 100 such samples. At that time, he prepared an "Interim Report Mesh Explants Pelvic Floor Repair".[138] His findings, summarized, were that "Foreign

[124] ETH.MESH.08315779 – September 24, 2012 Prolift +M Clinical Expert Report by Piet Hinoul
[125] Klosterhalfen, B., K. Junge, and U. Klinge, The lightweight and large porous mesh concept for hernia repair. Expert Rev Med Devices, 2005. 2(1): p. 103-17.
[126] Elmer C., Altman D., Ellstom Engh M., Axelsen S., Vayryen T., and Falconer C.; Trocar-Guided Transvaginal Mesh Repair of Pelvic Organ Prolapse. ACOG Vol. 113, No. 1, January 2009
[127] Elmer C, Blomgren B, Falconer C, Zhang A, and Altman D; Histological Inflammatory Response to Transvaginal Polypropylene Mesh for Pelvic Reconstructive Surgery. The Journal of Urology Vol. 181, 1189-1195, March 2009
[128] Jeffrey S, de Jong P: Mesh, Grafts and Kits in Pelvic Organ Prolapse Surgery: Where are we now? aSAUGR Vol. 6, No. 1 (2008)
[129] Blandon R, Gebhart J, Trabuco E, Klingele J, Complications from vaginally placed mesh in pelvic reconstructive surgery. Int Urogynecol J (2009) 20:523-531
[130] Kirschner-Hermanns R, Klinge U, Klosterhalfen B, Brehmer B, Heidenreich A; What can we learn from explanted slings and meshes in pelvic floor surgery? The Journal of Urology, 1772 Vol. 183, No. 4, Supplement (2010)
[131] G. Welty, U Klinge, M Stumpf, B Klosterhalfen, V Schumpelick (2000) Development of new mesh materials for hernia repair and clinical outcome of different polypropylene meshes. 35th Congress of the European Society for Surgical Research 1.-3.6.2000, Malmö, in European Surgical Research 32,S1,00: S. 3
[132] Altman D., Väyrynen T., Ellström Engh M., Axelsen S., Falconer C., (Transvaginal Mesh Group*) Anterior Colporrhaphy versus Transvaginal Mesh for Pelvic-Organ Prolapse. N Engl J Med 2011; 364:1826-36.
[133] Withagen MI, Vierhout ME, Milani AL; Does trocar-guided tension-free vaginal mesh (Prolift) repair provoke prolapse of the unaffected compartments? Int Urogynecol J. 2010 Mar; 21(3):271-8. Epub 2009 Nov 10.
[134] Klinge U, Junge K, Stumpf M (2003) Causes of recurrence after Lichtenstein tension-free hernioplasty (letter). Hernia 7: 100-101
[135] Krones CJ, Bohm G, Ruhl KM, Stumpf M, Klinge U, Schumpelick V (2003) Inguinal hernia on the Internet: A critical comparison of Germany and the U.K. Hernia. 2004,8: 47-52
[136] ETH.MESH.01819528: WW Customer Complaints – received from Carey Brennan
[137] ETH.MESH.01819528: WW Customer Complaints – received from Carey Brennan
[138] ETH.MESH.00006636: Klosterhalfen B., Interim Report Mesh Explants Pelvic Floor Repair

body tissue reaction followed by secondary fibrosis seems to play a special role in pelvic floor repair. This is important, because soft tissue coverage is thin in pelvic floor repair. Fibrosis and folding in this are inducing mesh erosions and ulcerations".

In June 2009, Prof. Klosterhalfen prepared another interim report regarding his histological examination of another 172 prolapse mesh explants concluding: "In summary, therefore, FBRs and secondary fibrosis seem to play a significant role in prolapse repair…Fibrosis inevitably leads to mechanical irritation, particularly when wrinkling occurs, and should be seen as the basic cause of mesh-induced erosion and ulceration…infection is commonly observed following erosion in the vaginal mucosa."[139]

Mesh erosions were becoming such a problem with Prolift that Dr. Peter Meier, a Principal Scientist with Johnson & Johnson Medical in Germany, prepared a 122-page "Clinical Evaluation Report – Mesh Erosions" in September 2010.[140] Dr. Meier reported that, "Mesh related complications may be associated with the mesh material used for reinforcement or the surgical procedure itself. Mesh material related to adverse events include infections, erosions, extrusions, mesh shrinkage, vaginal granulation tissue… Additionally, functional problems such as de novo urgency, urge incontinence, dyspareunia and nonspecific pelvic pain may also be observed in certain patient groups." The number one factor that Dr. Meier lists as causing mesh erosions is "pore size and porosity of the mesh" as discussed previously above.

As mentioned earlier, on May 18, 2011, Johnson & Johnson received the final PA Consulting Group report investigating mesh erosion. One of the things Johnson & Johnson asked these outside consultants to analyze was Dr. Meier's report from September 2010. In a 50-page report[141], PA Consulting reported that "Of the many variables that influence mesh erosion, pore size is listed first…transvaginal implantation has a higher risk of mesh erosion than trans-abdominal surgery…vaginal area carries many bacteria, so it is virtually impossible to insert mesh devices without contamination…If host cells cannot clear the bacteria on the mesh surface, the mesh is irreversibly contaminated and the bacteria may remain dormant for long periods with the possibility of establishing a tissue infection later…"

In addition, on December 21, 2011 Chris Vailhe prepared a paper for Ethicon entitled "Polypropylene Mesh for Pelvic Floor Repair (PFR) – Focus on Mesh Exposure – Road to Improvement".[142] Vailhe chose to focus the majority of the paper on "mesh exposure" as it was the highest percentage of adverse events.

The same holds true in hernia repair. In examining 1,000 explanted hernia meshes, infection and pain as the reason for mesh removal was most often seen in small pore meshes.[143]

VII. SAFER ALTERNATIVE DESIGN

[139] ETH.MESH.02157879-02157880: Klosterhalfen B., Intermediate Report – Prolapse Mesh Explants 6/2009
[140] ETH.MESH.00869977-00870098 Peter Meier "Clinical Evaluation Report – Mesh Erosions"
[141] ETH.MESH.02589032-02589079 PA Consulting report "Investigating Mesh Erosion in Pelvic Floor Repair"
[142] ETH.MESH.04038032-ETH.MESH.04038055 Chris Vailhe report "Polypropylene Mesh for Pelvic Floor Repair (PFR) – Focus on Mesh Exposure – Road to Improvement
[143] Klinge U, Klosterhalfen B. Modified Classification of surgical meshes for hernia repair based on the analyses of 1000 explanted meshes. Hernia 2012: 1-8

In 2001, Dr. Bridgette Hellhammer authored an internal document titled "Meshes in Pelvic Floor Repair – Findings from literature review and interviews with surgeons".[144] Her conclusions were that a pelvic floor repair using a mesh implant was plausible, and "A thinner mesh than the current Prolene mesh and with some elasticity would be well accepted. Vypro would meet these requirements. A totally nonabsorbable mesh with similar mechanical properties as Vypro would also be well accepted."

In 2002, Ethicon obtained a German patent No. DE 10043396C1 20.06.2002 for a PVDF surgical implant.[145] However, as it is now known, Gynemesh PS was chosen for Prolift, apparently for no other reason that it was "pre-ordained".[146] The physicians who developed the TVM technique (Cosson and Jacquetin), were aware of the complications associated with Prolift mesh and implored Ethicon to consider a different mesh material in 2004, before Prolift was launched for sale. In fact, Dr. Cosson advised Ethicon employee, Scott Ciarrocca in 2003 that the problems related to mesh are "more erosion, retraction".[147] In another email dated May 10, 2004, Ethicon employee Ophelie Berthier tells her co-workers that the inventors of the TVM technique, Pr. Jacquetin and Dr. Cosson are concerned about the shrinkage of mesh and its direct relationship to pain and dyspareunia.[148] It was well understood and recognized that the complications associated with Prolift mesh were occurring frequently enough to validate the need for a new material.

In February, 2004, during a meeting with Murty Vykarnam and Mora Melican, it was determined that erosion was still the primary concern of mesh products as it was the cause of scarring around the implant. It was also noted at that same meeting that contraction of the scar tissue has been reported and that contraction was linked to severe clinical complications.[149] The development of Prolift +M, a device utilizing a new material and new design for pelvic floor repair, eventually became known as "**Project Lightning**" and began in early 2006.[150]

Gene Kammerer, one of Ethicon's top R&D engineers advised his colleagues that the issue they needed solve was that of scar contracture of the mesh, which leads to: recurrence, pain, stiffness, erosion and dyspareunia. This information was known in April 2005, a month after Ethicon began to market and sell Prolift. Already in 2005, they were discussing whether Ultrapro was the better choice of material than the Gynemesh PS used in Prolift.

In a February 2007 PowerPoint presentation titled "Project Lightning Update", Ophelie Berthier, Marketing Manager EMEA described the new mesh material, Ultrapro, as a partially absorbable, monofilament, large pore, pliable, vaginally compliant mesh with little memory. Ms. Berthier states that, in general surgery (hernia), Ultrapro had proven to cause less inflammation, induce less fibrosis, have better integration to host tissues, maintain the mobility of the abdominal wall, have an outstanding biocompatibility, and improve patients' quality of life. During the first cadaver lab of Project Lightning, Dr. Lobodasch found a significantly smaller

[144] . ETH.MESH.02017169: Hellhammer, B., Meshes in Pelvic Floor Repair – Findings from literature review and interviews with surgeons. (2001)
[145] German Patent No. DE10043396C1 20.06.2002
[146] ETH.MESH.02270823: Email dtd 2/26/04 from Joshua Samon to Scott Ciarrocca, et al. Re: mesh implants – user needs
[147] ETH.MESH.02270724: Email dated July 19, 2003 from Cosson to Ciarrocca re mesh problems
[148] ETH.MESH.00584846: May, 2004 email string from Ophelie Berthier forwarding the concerns of Cosson and Jacquetin
[149] ETH.MESH.01220730 – Questions and Concerns raised at February 10, 2004 meeting
[150] ETH.MESH.00742724: PPT by Ophelie Berthier "Ethicon Women's Health & Urology: Project Lightning Update"

amount of "curling" in the mesh arms after implantation; after the second cadaver lab, Ethicon's Key of Opinion Leader, Dr. Vince Lucente stated, "Keep this one and throw the rest out…This feels like a piece of vaginal wall…"[151]

Ethicon also had a renewed interest in trying to develop Pronova (PVDF) sutures as a pelvic floor mesh. As a result, they began a new project to investigate this PVDF PFR design concept through a new project dubbed by Ethicon as "**Project Thunder**". August 14, 2007 Project Thunder meeting minutes reported that Ultra-light PP mesh was ready, Pronova in process. Pros and cons of Pronova to PP: Pro: Softness, Elasticity, better biocompatibility, less "aging" long time breakage, easier to manufacture and sterilize. Con: "May be more expansive (sic)". Preclinical on collagen coated PP started – histology results expected late September.[152]

Prolift +M using Ultrapro mesh was launched and received 510(k) clearance in May 2008, four years after the developers of the TVM technique suggested a different mesh material for use in the Prolift kit and 10 years after Ethicon had learned through the research of myself and my colleagues of safer alternative mesh designs. Also, despite the stated design and complication advantages of Prolift +M over Prolift, Ethicon continues to market and sell what they have essentially claimed as an inferior device.

As per a PowerPoint presentation, during the period from November 2010 to October 2011 **Project Thunder** was "killed" due to "tech push".[153] Although it is unclear as to what "tech push" infers, in multiple places, Ethicon seems to focus on the fact that PVDF costs more than PP.[154,155] In their May 9, 2008 Thunder MGPP presentation, one slide is particularly telling. It shows the Project Thunder products all out-performing Gynemesh PS and Ultrapro in every design attribute except one-cost.[156] Project Thunder was "killed" by Ethicon despite the fact that at multiple meetings, it was described as the "holy grail" of pelvic floor meshes, whereas Project Lightning (Prolift +M) was characterized as the "quick hit".[157]

The Ethicon Mesh Technology Center was also working on a "Exposure Reduction Mesh" specifically to address their need to reduce the occurrence of erosion in their products. In a 2010 PowerPoint presentation, it is noted that they need to "advance material science in PF repair by reducing mesh exposure (occurrence ~ 10%). [158] This again shows Ethicon's concern over erosions and the importance and reducing them. In 2011, during their EWHU Pelvic Floor Pipeline Update, it was again noted that they need to create a mesh to reduce the 10% occurrence of erosions. In this presentation, they state that phase I as "What is Mesh Exposure". This presentation comes six years after Prolift was marketed, Ethicon was still attempting to define what the term "exposure" meant and how that plays a part in the clinical implications of the mesh.

[151] ETH.MESH.00832555: Thunder Meeting Minutes dtd 4/12/07
[152] ETH.MESH.00869908: Thunder Meeting Minutes dated 8/14/07
[153] ETH.MESH.00562421: untitled PowerPoint update from November 2010 – October 2011
[154] ETH.MESH.02227224: PowerPoint Presentation dated 05/09/08 titled MGPP Thunder Decision Meeting
[155] ETH.MESH.00869908: Thunder Meeting Minutes dated 8/14/07
[156] ETH.MESH.02227224: PowerPoint Presentation dated 05/09/08 titled MGPP Thunder Decision Meeting
[157] ETH.MESH.01819833: GAT PPT
[158] ETH.MESH.071490420: WW ETHICON Mesh Technology Center Powerpoint Presentation

Ethicon internal documents demonstrate that 48% of complications were related to mesh. They were aware that the high erosion rates and mesh shrinkage relate to severe complications include pain, dyspareunia, recurrence and the necessity of additional surgeries. [159]

VIII. SUMMARY OF OPINIONS

Prior to launching Prolift for sale in the U.S., in their own documents, Ethicon acknowledged that the most important design requirements for a safe pelvic floor mesh product. According to their documents, Ethicon also acknowledged why these design requirements were so important in terms of patient safety.

However, as is also stated in their documents, Ethicon acknowledged the challenges and uncertainties of designing a safe mesh for the pelvic floor; that the design of Prolift did not meet all of their claimed optimal design requirements; and that as a result, this led to patient complaints and complications.

Ethicon has a long history of manufacturing surgical meshes that are intended to be permanently implanted by doctors in patients' bodies. They likewise have a long history of reported complications with their prosthetic meshes. With their experience from complications associated with some of the poor design characteristics in hernia meshes, Ethicon knew that poor design leads to poor outcome.

Through my team's collaborative efforts with Ethicon in the late 1990's and early 2000's, Ethicon learned that the development of an optimal surgical mesh design for any application has to consider first, the polymer; second, the biomechanics (physiological requirements) as to strength, elasticity and structural stability; and third, the structure of the device in terms of geometric design, knitting characteristics, fiber size and pore size. Ethicon knew that the result of these design considerations and choices would influence the tissue reaction, primarily the intensity of the inflammatory and fibrotic response, thereby directly affecting the biocompatibility of the device and thus the clinical outcome.

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However, despite these scientific realities, Ethicon failed to appropriately design and test its pelvic mesh kit, Prolift, to determine if these unintended and adverse events would occur when implanting Gynemesh PS permanently into a woman's pelvic tissues resulting in significant morbidity to women around the world. Regardless of whether or not Prolift is successful, on the one hand, by holding the pelvic organs in place, it is a disastrous failure if it leads to long-term serious complications like erosions, chronic pain, permanent sexual dysfunction, chronic wound healing issues and chronic infections, all of which have been seen and reported within the literature and in Ethicon's internal documents and its employees' deposition testimony.

Ethicon has stated repeatedly in its documents that it had a very poor understanding of the biomechanics of the pelvic floor, which apparently continues to this day. As such, it is impossible to establish reliable parameters for the design of the device. Furthermore, despite Ethicon's apparent knowledge of the significant amount of mesh shrinkage experienced by patients in whom Prolift had been implanted, the potential causes of mesh shrinkage, as well the

[159] ETH.MESH.00579556 : 2010 Mesh Platform Review

resultant patient complications that could occur as a result of this shrinkage, they did no testing nor made any design changes to Prolift in order to reduce the occurrence of this known and serious complication. It is my opinion to a reasonable degree of medical and scientific certainty, that the failure by Ethicon to properly study and/or make the necessary design changes to avoid this and the other safety hazards mentioned in this report was improper, irresponsible and threatened patient safety.

Ethicon's Gynemesh PS product was the same mesh used to create Prolift, Prosima and Gynesmesh PS flat mesh.[160] Since the material and material characteristics are identical among all of these products, it is my opinion, to a reasonable degree of medical and scientific certainty that the Prolift, Prosima and Gynemesh PS products are unreasonably dangerous and defectively designed to be placed in the pelvic tissues for prolapse repair.

Therefore, as stated throughout this report and in all of my deposition and trial testimony taken to date, it is my opinion to a reasonable degree of medical and scientific certainty that Ethicon's line of products that were made with Gynemesh PS mesh to treat pelvic organ prolapse were not specifically designed to function in the pelvic floor; they are over engineered, will create an intensified and chronic foreign body reaction; they have pores that are too small to resist fibrotic bridging and scar plate formation; and they will curl, rope and fray leading to particle loss and sharp edge. All of these design failures will, to a reasonable degree of medical and scientific certainty, cause an unnecessary risk of patient complications and injuries that include, but are not limited to, chronic pain, nerve entrapment, chronic foreign body reaction, erosion, infection, dyspareunia, recurrence, mesh contraction, and exposure.

I reserve the right to modify these opinions as necessary based upon any new or additional information or data that I may obtain or with which I am presented.

IX. PREVIOUS TESTIMONY

On November 10, 2014, my trial deposition testimony was given in *Dianne M. Bellew v. Ethicon, Inc., et al.*. All of my opinions and testimony contained within that transcript are incorporated herein by reference and attached as Exhibit "C". Additionally, as noted in Section X below, I have given testimony and provided expert reports in numerous Ethicon transvaginal mesh cases over the past few years. All of my testimony and opinions therein are hereby incorporated by reference.

I reserve the right to modify these opinions as necessary based upon any new or additional information or data that I may obtain or with which I am presented including, without limitation, any materials that I produce in response to Ethicon's requests.

[160] ETH.MESH.07229215; ETH.MESH.08310523; ETH-37788

X. EXHIBITS

My current curriculum vitae is attached as Exhibit "A"

All exhibits that will be used to support my finding and opinions are included above and listed below in Exhibit "B"

November 10, 2014 De Bene Esse Transcript attached as Exhibit "C"

Gross Expert Report attached as Exhibit "D"

Gross deposition attached as Exhibit "E"

Gross Trial Testimony as Exhibit "F"

Lewis Expert Report attached as Exhibit "G"

Lewis deposition attached as Exhibit "H"

Lewis Supplemental Expert Report attached as Exhibit "I"

Lewis Trial testimony attached as Exhibit "J"

Bellew Expert Report attached as Exhibit "K"

Corbet/Watkins Expert Report attached as Exhibit "L"

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Huskey/Edwards Expert Report attached as Exhibit "M"

Mullins Expert Report attached as Exhibit "N"

Mullins deposition attached as Exhibit "O"

Mullins Trial Testimony as Exhibit "P"

XI. RECENT TESTIMONY/EXPERT HISTORY

Linda Gross, et al. vs. Gynecare, et al.; Superior Court of New Jersey Law Division – Middlesex County Case No. MID-L-9131-08

Carolyn Lewis v. Ethicon, Inc., et al.; Southern District of West Virginia Charleston Division Case No. 2:12-cv-04301

Dianne M. Bellew v. Ethicon, Inc., et al.; Southern District of West Virginia Charleston Division Case No. 2:13-CV-22473

Kathryn Corbet et al. vs. Ethicon, Inc. et al.; Superior Court of New Jersey Law Division – Atlantic County Case No. ATL-L-2911-13 – Report Only

Dale Watkins et al. vs. Ethicon, Inc. et al.; Superior Court of New Jersey Law Division –Bergen County Case No. BER-L-13787-14 MCL – Report Only

Jo Huskey (2:12-cv-05201). Report Only

Tonya Edwards (2:12-cv-09972). Report Only

Mullins et al v. Ethicon, Inc., et al.; Southern District of West Virginia Charleston Division Case No. 2:12-cv-02952

XII. COMPENSATION

I am compensated for investigation, study and consultation in the case at the rate of $500.00 per hour.

This 17th day of November, 2015